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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,637	03/04/2002	Milton David Goldenberg	018733-1094	8273

26633 7590 07/28/2005

HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

EXAMINER	
HARTLEY, MICHAEL G	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 07/28/2005

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/086,637
Filing Date: March 04, 2002
Appellant(s): GOLDENBERG, MILTON DAVID

Patricia D. Granados
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09 May 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 183-193, 196 and 197 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

A substantially correct copy of appealed claims 183-193, 196 and 197 appears on pages 15-17 of the Appendix to the appellant's brief. The minor errors are as follows: claims 196 and 197 are not present in the appendix.

(9) Prior Art of Record

4,706,652	HOROWITZ	11-1987
4,932,412	GOLDENBERG	6-1990

5,256,395 BARBET ET AL. 10-1993

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 183, 187-189, 191-193, 196 and 197 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (USP 4,932,412) in view of Barbet (USP 5,256,395).

Goldenberg '412 discloses a method of detection of lesions during an intraoperative or endoscopic procedure comprising, 1) administering (injecting) to a patient an effective amount of a labeled antibody or antibody fragment which specifically binds a tumor antigen (such as, CEA, appellant's elected antigen) and detecting the presence of elevated levels of accreted label at the target site within 48 hours of said procedure, see column 2, lines 5-64. The methods further include combination therapies, such as, further including surgically removing lesions (e.g., tumors), the use of lasers, etc., see column 4, lines 24+, and laparoscopy, example 3. The antibody may be various types, including bispecific antibodies and fragments thereof, having CEA specificity, see columns 6-7. Various radionuclides may be used as the label, including In-111, appellant's elected species, see column 6.

Goldenberg fails to specifically disclose that the second binding site of the bispecific antibody binds a hapten and that a radiolabeled hapten is administered.

Barbet discloses a method of enhancing radioimmunodiagnosis and/or radioimmunotherapy by using a method comprising administration of a hapten which may be labeled with a radionuclide and using a bispecific antibody which has one binding site for a tumor and the other for the hapten, see columns 4-8 and example 4. Barbet teaches that the use of labeled hapten and bispecific antibody having binding sites for cancer antigen and the hapten improve the effectiveness of such radiodiagnostic/therapeutic procedures, see columns 8-9.

It would have been obvious to one of ordinary skill in the art to modify the methods of radiodiagnosis disclosed by Goldenberg by administering a radiolabeled hapten and a bispecific antibody having a second binding site to the hapten because it is known in the art that methods of radiodiagnosis using site specific radiolabeled antibodies can be made more effective by such a two-step approach of administering a bispecific antibody and a labeled hapten, wherein the bispecific antibody has a binding site for both the target (e.g., a cancer antigen) and the hapten, as shown by Barbet. One of ordinary skill in the art would have been motivated to use the improved means of accreting radiolabeled at the desired target site using hapten/bispecific antibodies as taught by Barbet to improve the effectiveness of the methods of radiodiagnosis disclosed by Goldenberg.

Claim 190 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goldenberg (USP 4,932,412) in view of Barbet (USP 5,256,395), as taken above, in further view of Horowitz (USP 4,706,652).

While Goldenberg and Barbet teach that combination therapies may be employed in the radiodiagnosis and radiotherapy of tumors, they fail to specifically teach that the combination therapy includes brachytherapy delivered via a catheter.

However, brachytherapy is well known in the art as a method of treating tumors.

Horowitz teaches that brachytherapy by administering radioactive seeds via a catheter provides advantages of safer implants that allow the patient to be discharged, see columns 1-2.

It would have been obvious to one of ordinary skill in the art to use brachytherapy as one of the combination therapies in the methods disclosed by Goldenberg because Goldenberg teaches that various combinations of cancer therapy may be used and brachytherapy is a well known therapy for the treatment of tumors that is administered via a catheter to provide safe and effective cancer treatment, while allowing the patient to be discharged from the treatment center, as shown by Horowitz.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 183-193, 196 and 197 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,387,350. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims of the patent are very similar to those of the pending application. For the most part, the patented claims are within the scope of the instant claims. The claims differ only slightly, for example, the patented claims specify that a clearing step using a specific

type of clearing agent within a specific time frame (within 24 hours), while the instant claims are open to a clearing step, which is present in dependent claims, but none of the pending claims recite the time frame (as in the patented claims). Since the claims are open to when the clearing agent may be injected, it would have been obvious to one of ordinary skill in the art to administer the clearing agent anytime prior to the procedure recited in the preamble, which is up to 48 hours after administration of the first component so that the clearing is effected prior to completion of the method to obtain the advantage of clearing the unbound antibody. Thus, it would have been obvious to administer the clearing agent within 48 hours, which specifically encompasses the, "within 24 hours" time frame, as claimed in the patent. Also, the dependent claims of the pending application state that the clearing agent may the same as those claimed.

(11) Response to Argument

Appellant's arguments in the appeal brief filed 5/9/2005 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

Appellant asserts that Goldenberg does not teach all that the examiner states, that is, Goldenberg does not teach all of the elements except that hapten system. Appellant asserts that Goldenberg only shares the preamble with claim 183.

Part of this argument is agreed upon. Goldenberg is used mainly to show the same method, as disclosed in the preamble of claim 183 is known in the art. Goldenberg also is relied upon to show the limitations in the rejected dependent claims, such as, wherein the target antigen is a tumor (claims 187), wherein the method further includes surgical removal of the tumor or ionizing radiation (claims 188-189), laparoscopy, and the various labels, e.g., radiolabels in the dependent claims. Goldenberg is mainly relied upon to show the method, as recited in the preamble with known radioimmunodiagnostic methods, i.e., radiodiagnosis with

the use of radiolabeled antibodies. Goldenberg discloses such a method using mainly a one-step targeting procedure (direct targeting) using various antibodies or fragments thereof. The difference, as asserted by the examiner, between Goldenberg and the claimed invention, is the use of the two-step targeting procedure (indirect targeting). The two-step procedure is characterized mainly by steps (a) and (b) in claim 183. Part (c), which is mainly the detection of the label, is present in any radioimmunodiagnostic method. The two-step targeting procedure uses a bispecific antibody and a labeled hapten to target the site, as opposed to a labeled antibody, as shown by Goldenberg (a one-step targeting procedure). This is the crux of the examiner's position. That is, that it would have been obvious to one of ordinary skill in the art to modify the method of close-range detection of a lesion during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure using a one-step radioimmunodiagnostic procedure, as disclosed by Goldenberg, by using a two-step radioimmunodiagnostic procedure as taught by Barbet, because Barbet teaches that using a two-step procedure (i.e., the use of a bispecific antibody and labeled hapten to target the site, as shown in steps a-c in claim 183) provides the advantage of improving the effectiveness of radioimmunodiagnostic procedures, as compared to the known one-step procedure. The change of the one-step procedure as disclosed by Goldenberg to a two-step procedure, as taught as being advantageous by Barbet, would produce the instant invention.

Appellant further asserts that Goldenberg does not teach the use of antibody fragments of 85,000 Daltons or less.

This is not found persuasive because Goldenberg clearly teaches the use of Fab and Fab' fragments (see column 6, lines 50-54), which are inherently in this size range (as supported by Barbet, see column 6, lines 25-36). However, it is the antibody fragments and labeled hapten disclosed in the two-step targeting procedure of Barbet that are critical to the

obviousness rejection. Barbet clearly teaches the use of antibody fragments in this size range, as shown in column 6, lines 25-36.

Appellants further argue that Goldenberg discloses a large number of antibodies, thus, causing a picking and choosing situation, and in addition, that the type of antibody used is not relevant in Goldenberg, while the antibody of the instant invention is relevant.

While Goldenberg does teach the use of a large number of antibodies, this argument somewhat distorts the combination of the references because both Goldenberg and Barbet teach the use of antibody fragments as claimed. It is admitted that Goldenberg discloses the use of a large number of antibodies. This is simply because it is known in the art that various antibodies, and fragments thereof may be used in methods of radioimmunodiagnostics as art recognized equivalents. It is clear from the disclosures of both Goldenberg and Barbet, that it is recognized in the art that antibody fragments (such as, Fab and Fab' fragments which would have a MW as claimed) are clearly useful and/or art recognized equivalents to other antibodies in methods of Goldenberg and Barbet. Barbet clearly discloses the use of such antibody fragments (having a MW of 50,000 Daltons) in the same field of endeavor in a two-step procedure as claimed (col. 6, lines 25-36); while Goldenberg also teaches that the use of such antibody fragments is commonplace in radioimmunodiagnostics.

Appellant argues that Goldenberg does not teach the detection step within 48 hours of administration of the first injection and that the time frame in Goldenberg is different from the time frame as claimed.

This is not found persuasive because this time frame is for imaging after administration of the agents used for radioimmunodiagnostics. Clearly, the 2-72 hours after the administration of the second antibody encompasses the within 48 hours of the first antibody, as claimed. This is further shown in example 3, wherein the first antibody is administered, then 6 hours later the

second antibody is administered, and then after 16 hours imaging is performed. This is a total of 16+6=22 hours, which is within the scope of the claimed time frame. The time frames for imaging after administration of radiolabeled reagents in methods of radioimmunodiagnostics are well known and are well within the claimed range. This is due to the half-life of radiolabels, which decay over time. Thus, imaging is performed in these methods as soon as targeting is achieved. This is not only disclosed by Goldenberg, which encompasses a range as claimed, but is also well known in the art, as shown by Barbet, which discloses that imaging is performed within a few hours, at a time when optimum localization has been achieved, see column 9, lines 7+. Appellant's argument concerning the time frame of Goldenberg to that claimed, as comparing apples to oranges is somewhat true, but not relevant. This is because Goldenberg discloses a one-step targeting approach (or direct targeting), as compared to the two-step targeting method as claimed, the time frames between what is administered, i.e., (the so-called first antibody) can be stated to be "different". This is somewhat a manipulation of time frames that are actually occurring, due to the difference between the one-step and two-step procedures of Goldenberg and Barbet, respectively. Goldenberg, as well as, Barbet teach that it is standard in the art to perform imaging in a time frame that is within the scope of that claimed after starting the administration of the agents in radioimmunodiagnostics. Barbet clearly teaches imaging after a few hours, which is within the claimed range, see column 9, lines 7-17. The time frame set forth in Barbet is a comparison of apples to apples, as it is the same time frame specifically recited in the claims. Barbet teaches the advantages of using a two-step targeting approach (or indirect targeting using a bispecific antibody and labeled hapten) to improve the effectiveness of radioimmunodiagnostic procedures, such as, those of Goldenberg and the time frame is the same as claimed, as it would be in the methods of Goldenberg. Further, appellant has not suggested or shown any criticality in this time frame, as compared to the overlapping time

frames of the prior art. Many of the arguments appear only to be directed toward what is taught by Goldenberg, but one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is Barbet that discloses the two-step targeting approach (indirect targeting using a bispecific antibody and labeled hapten), as set forth in steps a-c in claim 183, and Barbet specifically teaches that the two-step method is an improvement over the one-step method, as disclosed by Goldenberg. The arguments do not appear to relate to what the prior art teaches as a whole, but only specific embodiments of the primary reference that are different from the claimed invention.

Appellant also asserts that the combination is wrong as a matter of law because the combination of Goldenberg and Barbet would not arrive at the instant invention.

This argument is not clear, as it is conclusionary because there is nothing specifically asserted to be missing from the combination, as compared to the instant claims. There is much discussion on what is missing from Goldenberg, but it is unclear how, even when combined, one would not arrive at the invention, as nothing is specifically pointed out as missing from the combination.

In sum, Goldenberg discloses a one-step targeting or direct targeting approach in a method of radioimmunodiagnostics, as generally recited in the preamble and some of the dependent claims. Barbet, which is in the same field of endeavor, that is, methods of radioimmunodiagostics, teaches that a two-step targeting approach or indirect targeting approach in methods of radioimmunodiagostics is an improvement over the direct targeting as it increases the uptake and localization of the labeled tracers (i.e., since the labeled molecule is smaller, it has increased localization and clearance), see column 2, lines 16+ and columns 8-9 of Barbet. Therefore, it would have been obvious to one of ordinary skill in the art to use the two-step or indirect targeting approach disclosed by Barbet in the general methods of

radioimmunodiagostics disclosed by Goldenberg to take advantage of the various advantages of the two-step approach that are known in the art, as taught by Barbet. The use of a two-step radioimmunodiagnostic procedure, as taught by Barbet, in the method of Goldenberg would arrive at this instantly claimed invention, as this modification would incorporate steps a-c (which are disclosed in the invention of Barbet) in the methods disclosed by Goldenberg, which are drawn to the same general radioimmunodiagnostic methods as claimed.

Double Patenting

Appellant's request to hold the obviousness type double patenting rejection in abeyance until indication of allowable subject matter is acknowledged. The rejection is maintained for reasons of record.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Michael G. Hartley
Primary Examiner
Art Unit 1618

Michael Hartley
July 21, 2005

THURMAN K. PAGE, M.A., J.D.
SUPERVISORY PATENT EXAMINER

Conferees:
Thurman K. Page, Supervisory Patent Examiner
Gary Kunz, Supervisory Patent Examiner

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001